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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,197	07/31/2003	Thomas P. Maduskuie	PH 7423 NP	9821

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EXAMINER	
HOFFMAN, LEXINGTON A	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,197	MADUSKUIE, THOMAS P.	
	Examiner	Art Unit	
	Lexington A. Hoffman	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-9* is/are allowed.

6)☒ Claim(s) *10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/23/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims reach out to the treatment of inflammatory diseases, and although there are numerous diseases of varied etiology listed in the specification, applicant does not define what he considers to be an inflammatory disease.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 14 reaches out to combinations of the instant compounds with other pharmaceuticals, including TNFά inhibitors. While examples of the intended embodiments of the other medications to be combined with the instant invention were listed (COX-2 inhibitors, e.g.), no such examples were given for TNFά inhibitors.

Claims 10-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. *nature of the invention*

The instant invention is drawn to hydroxamic acid derivatives as inhibitors of matrix metalloproteinases (MMP), or TNF-ά converting enzyme (TACE), or a combination thereof, pharmaceutical compositions containing the same, and methods of using the same.

b. *state of the prior art and level of skill of the artisan*

Different MMPs and TACE are known to have varied physiologic effects. "MMPs and TACE assume independent, parallel, or opposite pathological roles in cancer, arthritis, and several other diseases." (Lukacova, et al. "A Comparison of Binding Sites of Matrix Metalloproteinases...", Journal of Med. Chem., 2005, 48 2361-2370 (quoted line from abstract). However, the connection between MMPs and TACE and specific disease processes (especially the diverse list disclosed in claim 13), as well as their usefulness as therapeutic targets is neither simple nor well established.

For example, vasculitis may be a result of overexpression of TNF-ά, and systemic lupus erythematosus may be result of its underexpression (Mackay, et al., "Autoimmune Diseases", New Engl. J. of Med., 345(5), Aug, 2001., p. 345, figure 2) yet applicant claims the inventive compounds can treat both diseases by inhibiting TACE.

"There are also more than 20 identified MMPs, with different specificities of structure, location, and substrate" (Daheshia, "Therapeutic inhibition of matrix metalloproteinases...", Current Medical Research and Opinions, vol. 21., no. 4, 2005, p. 588, bottom of left column). Levin wrote "...the different selectivity profiles offered by these MMP/TACE inhibitors may allow the determination of *which* metalloprotease [emphasis added], of group of metalloproteases, must be inhibited for the safe, long-term treatment..."(Levin, "The design and synthesis of aryl hydroxamic acid inhibitors of MMPs and TACE", Current Top. Med. Chem., 2004;4(12) (line from abstract).

Additionally, Mannello wrote "Although preclinical trials [of MMP inhibitors] were so compelling to encourage several clinical trials, the past years have seen a consistent number of disappointments and limited success." (Manello, et al., "Matrix metalloproteinase inhibitors as anticancer therapeutics", Current Cancer Drug Targets, 2005 June;5(4): (line from abstract).

Finally, Daheshia (prev. citation) wrote "...the consequence[s] of MMP inhibition [on] the protective immunity and tissue repair should be a concern to be investigated because these enzymes have natural biological functions related to various substrates and numerous tissues."(p. 592).

Due to the high degree of specialization of medical practitioners, physicians tend to treat diseases either of similar etiology or with similar target organs (e.g., there are ophthalmologists, rheumatologists, vascular surgeons, etc.) and presumably they are quite skilled in their field. Even one of exceptional skill, though, could not be expected

to treat all of the diseases listed in claim 13 due to their various etiologies and anatomic targets.

c. *predictability/unpredictability of the art*

The high degree of unpredictability in the art is clear. Applicant's own structurally similar compounds can vary in K_i by 2 orders of magnitude. When one combines different medications with different modes of action and different physiologic targets, as claimed in claim 14, results become even more unpredictable due to possible synergistic, antagonistic, or toxic effects of the combination.

d. *amount of guidance/working examples*

The preparation of example compounds was described in the specification. Applicant describes assays of TNF and MMP inhibition, but does not describe the effects of specific compounds, instead disclosing ranges of data ($\leq$1μM, for example) for "preferred" compounds, "more preferred" compounds, and "still more preferred" compounds, without defining these terms. The applicant also does not describe which compounds are effective at inhibiting which MMP.

e. *breadth of the claims*

Applicant's assertion that the inventive compounds would be effective in treating all the diseases disclosed is not commensurate with the scope of the objective enablement. The claims embrace diseases of divergent etiology, including diseases in which the immune system is overactive (rheumatoid arthritis) and barely active at all (HIV infection). They embrace infectious disease (Lyme disease), neoplastic disease (solid tumor growth), vascular disease (aortic aneurism), degenerative disease (macular

degeneration), and diseases which may be traumatic or iatrogenic in origin (hemorrhage and post-radiation asthenia). Claim 14 further embraces "autoimmune disease", which is not a single disease entity but an entire class of disease; a class whose exact members are still a matter of debate. Claim 14 also reaches out to "coagulation" which is not a disease but a physiologic process necessary to maintain homeostasis, and causes disease when it is either excessive or deficient. Given that the claims embrace diseases of divergent and sometimes conflicting pathology, and that no known drug is able to treat all these conditions, the breadth of the claims is not enabled by the specification.

f. *quantity of undue experimentation*

Since insufficient guidance and teaching have been provided by the specification, one of ordinary skill in the art is unable to use the inventive compound as claimed without resorting to undue experimentation.

Allowable Subject Matter

Claims 1-9 are allowed. While the prior art discloses compounds that are similar to the instant, none disclose the exact structures. The motivation to modify the prior to arrive at the instant is lacking.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lexington A. Hoffman whose telephone number is 571-272-4328. The examiner can normally be reached on Monday-Friday 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecelia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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10/21/05 LH

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